Risk of lymphohematologic malignancies in patients with chronic plaque psoriasis: A systematic review with meta-analysis

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Background: The association between chronic plaque psoriasis and lymphohematologic malignancies (LHMs) remains controversial.

Objective: To investigate the risk of LHMs in patients with psoriasis according to the best evidence.

Methods: A systematic review and meta-analysis of observational cohort studies was undertaken to assess the association of psoriasis with different LHMs. A literature search for relevant studies was performed on February 28, 2021. The random-effects model in conducting meta-analyses was applied. To evaluate the risk of bias, the Newcastle-Ottawa Scale was employed.

Results: A total of 25 observational studies were selected, comprising collectively 2,501,652 subjects. A significantly increased risk for LHM (hazard ratio [HR], 1.55; 1.24-2.94) and lymphoma (HR, 1.27; 1.08-1.50) in patients with moderate-to-severe plaque psoriasis compared to the general population was found. In detail, increased risks for Hodgkin lymphoma (HR, 1.71; 1.27-2.30), non-Hodgkin lymphoma (HR, 1.27; 1.08-1.50), multiple myeloma (HR, 1.32; 1.03-1.69), and leukemia (HR, 1.28; 1.00-1.65) were found. The risk of cutaneous T-cell lymphoma was markedly augmented in patients with psoriasis (HR, 6.22; 3.39-11.42).

Limitations: Possible ascertainment bias related to the diagnosis of LHMs.

Conclusion: The increased risk of LHMs, particularly cutaneous T-cell lymphoma, in patients with psoriasis could be related to exposure to systemic immunosuppressive therapies, comorbidities, and sustained immune activation, particularly in the skin. (J Am Acad Dermatol 2022;86:86-96.)

Key words: leukemia; lymphoma; meta-analysis; mycosis fungoides; oncology; psoriasis neoplasms.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory disease (IMID) that has been associated with a slightly increased risk of certain cancers, particularly keratinocyte, lung, and bladder cancer.[1] Psoriasis is also commonly associated with other IMIDs, such as psoriatic arthritis and inflammatory bowel diseases.[2] Patients with inflammatory bowel disease have an higher risk of developing lymphohematologic malignancies (LHMs), more specifically leukemia in ulcerative colitis and lymphoma in Crohn's disase.[3] Moreover, an increased risk of LHMs also has been reported in patients with other IMIDs, such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, and dermatomyositis.[4-6]

In a genetically predisposed background, immune signaling dysregulation, inflammatory environment with chronic activation of B and/or T lymphocytes can contribute to the pathogenesis of

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lymphoproliferative disorders.[3] The association between psoriasis and LHMs remains debatable.[6,7] The objective of the study was to appraise the association between psoriasis and LHMs according to the best evidence available.

METHODS

The present study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis of Observational Studies in Epidemiology guidelines.[8,9] The study protocol was registered with PROSPERO, registration number CRD42021240115.

Search strategy

Electronic searches were performed on PubMed and Ovid databases using the following exact string: "(psoriasis) AND (lymphoma OR leukaemia OR mycosis fungoides)" from their respective inceptions to February 28, 2021. There were no restrictions on language, geographic area, or publication status. References of the selected publications were additionally screened for other eligible records.

Selection criteria

Eligible studies included in the meta-analysis were observational cohort studies investigating the risk of developing LHMs in a time-dependent manner in patients with chronic plaque psoriasis compared to controls without psoriasis. Case-controlled and cross-sectional studies and narrative reviews were excluded. The hazard ratio (HR), standardized incidence ratio (SIR), incidence rate ratio, or risk ratio were selected as measures of association, whereas the odds ratio was excluded because it is a risk measure that does not consider the exposure time.

The subtypes of LHMs selected for the study were Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), cutaneous T-cell lymphoma (CTCL), mycosis fungoides (MF), multiple myeloma, and leukemia. Two authors (FB and PG) independently retrieved the records to assess eligibility by reviewing titles and screening abstracts. Full texts of potentially eligible studies were examined. A third senior author (GG) was consulted to resolve any disagreements.

Data extraction

By using an extraction form, the following data from the selected studies were collected: study design, last name of first author and publication year, risk estimates for the association between chronic plaque psoriasis and LHMs (HR, incidence rate ratio, SIR, or risk ratio with a 95% confidence interval [CI]). The association between psoriasis and LHMs was investigated by stratifying the disease severity in mild and the moderate-to-severe form. Finally, a subgroup analysis for mild and moderate-to-severe psoriasis was conducted.

Evaluation of risk of bias

The Newcastle-Ottawa Scale was used to assess the risk of bias of the studies by analyzing the following 8 items: representativeness of exposed cohort, selection of nonexposed cohort, ascertainment of exposure, outcome of the interest declared at the start of the study, comparability of the cohort, assessment of outcome, follow-up duration, and adequacy of follow-up of cohorts.[10]

Statistical analysis

The analysis was conducted using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment to reduce the potentially confounding risk factors. A meta-analysis was performed, assessing the overall risk of LHMs, of any lymphoma without leukemia, and of HL, NHL, CTCL/MF, multiple myeloma, leukemia in patients with psoriasis. Studies reporting risk ratio were excluded from quantitative analysis. Additional SIR with their 95% CI on the assumption of a Poisson distribution were calculated in the studies providing raw data.

For cohort studies, SIR was considered as HR.[11] The DerSimonian-Laird random-effects model in conducting meta-analyses was applied, as this methodology considers any differences between studies even if there is no statistically significant heterogeneity. The statistical heterogeneity across the included studies was evaluated using the I^2 analysis, which provides an estimate of the percentage of variability across studies that is due to heterogeneity rather than chance alone. Visual inspection of the

CAPSULE SUMMARY

- An overall increased risk of lymphohematologic malignancies was found in patients affected by chronic immune-mediated inflammatory diseases, including psoriasis.
- Patients with moderate-to-severe plaque psoriasis have a moderately increased risk for developing any lymphohematologic malignancy. The risk of cutaneous T-cell lymphoma is more than 6 times higher compared to controls.

Abbreviations used:

CI: confidence interval
CTCL: cutaneous T-cell lymphoma
HL: Hodgkin lymphoma
HR: hazard ratio
IMID: immune-mediated inflammatory disease
LHM: lymphohematologic malignancy
MF: mycosis fungoides
NHL: non-Hodgkin lymphoma
SIR: standardized incidence ratio
TNF: tumor necrosis factor

forest and funnel plots was used to investigate the possibility of statistical heterogeneity and publication bias, respectively. To explore the possible sources of the (expected) heterogeneity among the eligible studies and to test the robustness of the observed associations, we conducted subgroup analyses by severity of psoriasis.

RESULTS

Characteristic of included studies

All of the articles were screened according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart presented in Supplemental Fig 1 (available via Mendeley at https://data.mendeley.com/datasets/trrfthg8nx/1). After removing duplicates, a total of 1384 records were identified through electronic database searches and were screened by title and abstract. After scanning the titles and abstracts, 1334 citations were excluded. Full texts of the remaining 50 original records were examined. A total of 25 records were excluded because they were case/control studies or reporting outcomes were not relevant. Twenty-five records, comprising a total of 2,501,652 study subjects, were included in the qualitative analysis and 23 records were included in the quantitative analysis.[6,12-35] The characteristics of the included cohort studies are listed in Table I.[6,12-35]

Association of chronic plaque psoriasis with lymphohematologic malignancies

A meta-analysis of 23 studies was conducted. Twelve provided data for any unspecified lymphoma (HR, 1.27; 95% CI, 1.08-1.50) and 5 for any unspecified hematologic malignancy (HR, 1.55; 95% CI, 1.24-2.94) (Fig 1). Moderate statistical heterogeneity was found across the studies included in the former (I^2 = 56%), while no heterogeneity was found among the latter (I^2 = 0%). A subsequent meta-analysis of the studies investigating the association between psoriasis and specific subtypes of lymphoma was conducted; in particular, 6 studies for HL, 12 for NHL, and 7 for CTCL/MF. Significantly increased risk was found for HL (HR, 1.71; 95% CI, 1.27-2.30), NHL (HR, 1.27; 95% CI, 1.08-1.50), and CTCL/MF (HR, 6.22; 95% CI, 3.39-11.42) (Figs 2 and 3). Moderate statistical heterogeneity was found across the studies of the first 2 analyses (I^2 = 39% and I^2 = 56%), respectively, while substantial heterogeneity was found in the latter (I^2 = 83%). Finally, the risk for multiple myeloma and leukemia was assessed in 2 and 8 studies, respectively. An increased risk was found for multiple myeloma (HR, 1.32; 95% CI, 1.03-1.69; I^2 = 0%), and leukemia (HR, 1.28; 95% CI, 1.00-1.65, I^2 = 6%) (Fig 4). Most of the patients included in the studies had a moderate-to-severe psoriasis, and only 3 of 25 studies investigated the risk of LHMs also in patients with mild disease. Subgroup analysis allowed to reduce heterogeneity and showed a positive trend between psoriasis severity and risk of CTCL (Supplemental Table I).

Risk of bias

All 25 studies included were rated at low risk of bias in all the domains except for the representativeness of exposed cohort, outcome of interest declared at the start of the study, assessment of outcome, and duration of follow-up. The outcome ascertainment and exposure definition were based on validated administrative general practitioner database in 2 studies, which may give rise to an ascertainment bias.[6,20] The vast majority of the studies compared the group of patients with psoriasis to the general population, adjusting for age, gender, and treatment. Other rarer variables included in the adjusted models were socioeconomic status, ethnicity, diabetes, hypertension, dyslipidemia, income levels, and area of residence. Most of the studies showed a mean follow-up of at least 5 years (range, 1.5-30). The results of Newcastle-Ottawa Scale scoring were reported as an aggregate score (ranging from 0 to 8) as the sum of the scores of the 8 binary responses. According to the Newcastle-Ottawa Scale, the average aggregate score across the studies was 7.4 ± 0.8 (Supplemental Fig 2). Funnel plots are shown as Supplemental Figures 3 to 9.

DISCUSSION

We found that patients with moderate-to-severe plaque psoriasis have a slightly increased risk for developing any LHMs compared to controls. When considering the specific subtypes of LHMs, the increased risk ranges from 1.71-fold for HL, 1.27-fold for NHL, 1.32-fold for multiple myeloma, 1.28-fold for leukemia, and more than 6 times for CTCL/MF.

Different hypotheses may explain the higher likelihood of LHMs in patients with psoriasis,

Table I. Characteristics of the studies

Reference	Study design	Psoriasis patients, N	Control patients, N	Mean follow-up, years	Risk for Hodgkin lymphoma	Risk for non-Hodgkin lymphoma	Risk for any lymphoma	Risk for CTCL/MF	Risk for multiple myeloma	Risk for leukemia	Risk for LHM
Asgari et al, 2016[12]	Cohort study	5889	National population	5.5	-	-	HR 1.01 (0.38-2.70)	-	-	-	-
Boffetta et al, 2001[13]	Population-based cohort study	9773	National population	10.6	SIR 0.36 (0.01-2.02)	SIR 1.42 (0.89-2.15)	SIR 1.47 (0.79-2.74)	SIR 19.3 (6.22-45.1)	SIR 1.22 (0.61-2.19)	SIR 1.33 (0.73-2.42)	SIR1.40 (0.92-2.16)
Brauchli et al, 2009[14]	Cohort study	33,760	34,001 matched control	4.6	-	-	IRR 1.76 (1.19-2.58)	-	-	IRR 1.89 (1.21-2.94)	IRR 1.89 (1.21-2.94)
Chen et al, 2001[15]	Retrospective population-based cohort study	3686	200,000 randomly selected	1.5-10 (range)	-	-	-	-	-	-	HR 2.21 (0.97-5.02)
Chiesa Fuxench et al, 2016[16]	Population-based cohort study	198,366	937,716	6.1	-	-	HR 1.23 (1.09-1.39)	HR 3.59 (2.35-5.49)	-	HR 0.95 (0.85-1.05)	-
Fallah et al, 2014[17]	Population-based cohort study	131,215	General population	7.1	-	SIR 1.4 (1.2-1.6)	-	-	-	-	-
Fallah et al, 2014[18]	Population-based cohort study	933,667	General population	7.1	SIR 1.9 (1.3-2.6)	-	-	-	-	-	-
Frentz and Olsen, 1999[19]	Cohort study	6905	National population	9.3	-	SIR 1.4 (0.8-2.2)	-	SIR 15.1 (4.1-38)	-	SIR 0.9 (0.5-1.6)	SIR 1.28 (0.79-2.07)
Gelfand et al, 2003[20]	Population-based cohort study	2718	General population	3.8	-	-	HR 2.94 (1.82-4.74)	-	-	-	-
Gelfand et al, 2006[6]	Cohort study	153,197	765,950	4.5	HR 1.48 (1.05-2.08)	HR 1.14 (0.96-1.35)	HR 1.35 (1.17-1.55)	HR 4.34 (2.89-6.52)	-	-	-
Gu and Nordstrom, 2017[21]	Cohort study (pediatric)	9045	General population (pediatric)	1.6	-	-	SIR 5.42 (1.62-12.94)	-	-	-	-
Hannuksela et al, 1996[22]	Cohort study	530	General population	11	-	SIR 2.94 (0.36-10.6)	-	-	-	-	-
Hannuksela-Svahn et al, 1999[23]	Cohort study	944	General population	7.6	-	SIR 3.7 (1.2-8.6)	-	-	-	-	-
Hannuksela-Svahn et al, 2000[24]	Cohort study	5687	General population	14	SIR 3.3 (1.4-6.4)	SIR 2.2 (1.4-3.4)	SIR 2.4 (1.2-5.2)	-	-	-	-
Ji et al, 2009[25]	Cohort study	15,858	National population	10 (Median)	-	SIR 1.31 (1.00-1.69)	-	-	-	SIR 1.47 (0.97-2.14)	-
Kamstrup et al, 2018[26]	Population-based cohort study	58,138	National population	5	HR 1.50 (1.01-2.23)	HR 1.02 (0.84-1.24)	-	HR 1.66 (0.88-3.13)	-	-	-
Kimball et al, 2015[27]	Cohort study	2510	General population	5	-	SIR 0.28 (0.03-1.02)	-	-	-	-	-

Continued

Table I. Cont'd

Reference	Study design	Psoriasis patients, N	Control patients, N	Mean follow-up, years	Risk for Hodgkin lymphoma	Risk for non-Hodgkin lymphoma	Risk for any lymphoma	Risk for CTCL/MF	Risk for multiple myeloma	Risk for leukemia	Risk for LHM
Lee et al, 2012[28]	Retrospective population-based cohort study	7061	General population	4.8	-	-	SIR 2.3 (1.15-4.60)	-	-	-	-
Lee et al, 2019[29]	Population-based cohort study	892,086	National population	8	-	-	HR 1.34 (1.15-1.56)	-	HR 1.33 (1.02-1.73)	HR 1.25 (1.02-1.55)	-
Li et al, 2016[30]	Cohort study	1404	63,586	6	-	HR 1.03 (0.59-1.78)		-	-	-	-
Margolis et al, 2001[31]	Cohort study	17,620	259,808	2	-	-	RRR 2.11 (1.63-2.74) RRR 7.95 (4.94-12.79)	-	-	-	-
Olsen et al, 1992[32]	Cohort study	6910	National population	5.1	RR 1.0 (0.1-4.9)	RR 1.4 (0.7-2.7)	-	-	RR 0.3 (0.0-1.6)	RR 1.2 (0.5-2.2)	-
Paul et al, 2003[33]	Cohort study	1252	General population	5	-	-	SIR 2.0 (0.2-7.2)	-	-	SIR 7.3 (1.5-21.5)	-
Polachek et al, 2021[34]	Cohort study	2051	General population	15	-	-	-	-	-	-	SIR 1.49 (0.85-2.43)
Stern, 2006[35]	Cohort study	1380	General population	30	-	-	IRR 3.49 (1.25-9.79)	-	-	-	-

CTCL, Cutaneous T-cell lymphoma; *HR*, hazard ratio; *IRR*, incident rate ratio; *LHM*, lymphohematologic malignancy; *MF*, mycosis fungoides; *RR*, rate ratio; *RRR*, relative rate ratio with 95% CI; *SIR*, standardized incidence ratio.

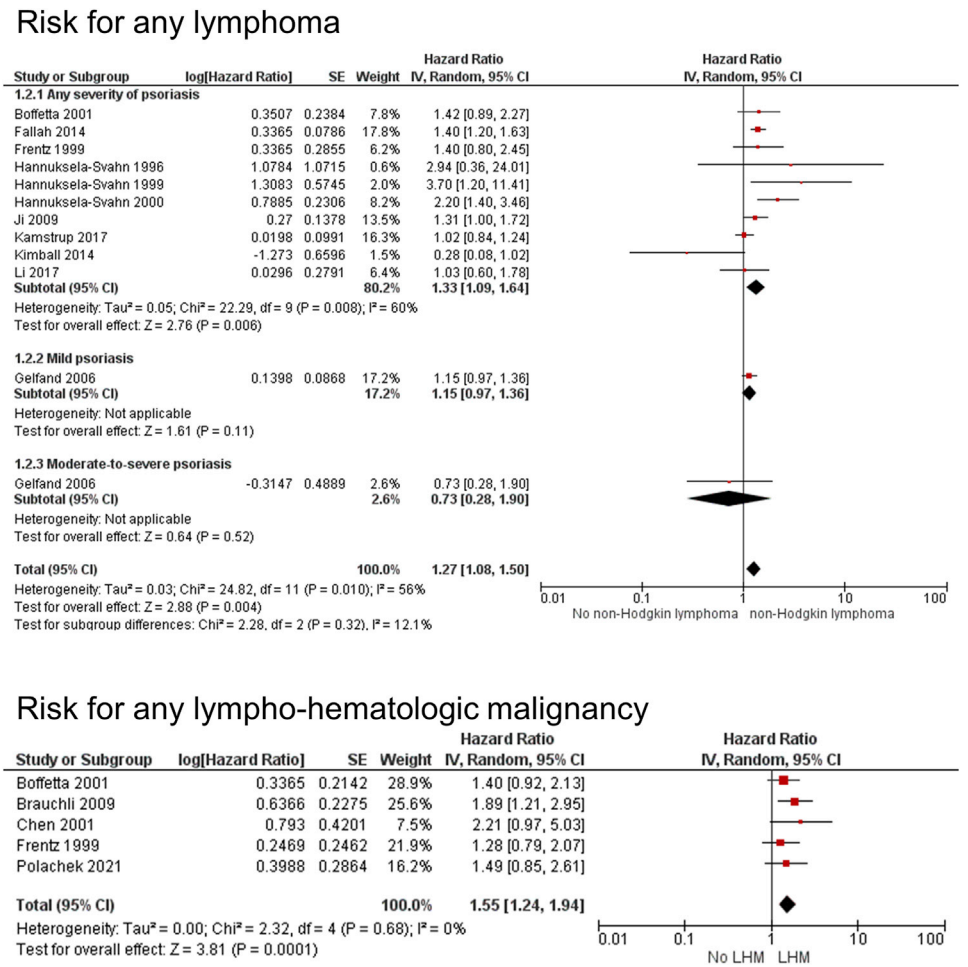

Fig 1. Forest plot for cohort studies investigating the risk of any lymphohematologic malignancy and any lymphoma in patients with psoriasis compared to general population. *LHM*, Lymphohematologic malignancy.

including a genetic background, exposure to systemic immunosuppressants, comorbidities, unhealthy lifestyles, and a chronic inflammatory state with sustained activation of lymphocytes.

Whether long-term exposure to selected immunosuppressive drugs may affect the risk of LHMs is debated. High-dose and long-term cyclosporine treatment has been associated with an increased risk of NHL and/or lymphoproliferative disorders correlated to Epstein-Barr virus infection in transplant recipients.[36] Patients with psoriasis treated long term with cyclosporine showed a higher risk of lymphoma compared to those who received shorter courses.[33] In contrast, acitretin is likely protective against a variety of solid and hematologic malignancies.[37] Although earlier studies suggested a slightly increased risk of lymphoma in patients treated with methotrexate, later investigations did not confirm this association.[38,39]

Methotrexate is currently employed as a treatment of selected cutaneous lymphomas.[40] The risk of LHMs in patients receiving tumor necrosis factor (TNF)-α inhibitors is uncertain. TNF-α inhibitors negatively affect the activation and function of NK cells by impairing the immunosurveillance against B-cell lymphoma.[41] Earlier studies reported an increased risk of lymphoma associated with the use TNF-α inhibitors in patients with rheumatoid arthritis; however, later investigations have failed to confirm this finding.[42] A recent meta-analysis reported an increased risk of lymphoma in patients with inflammatory bowel disease treated with TNF-α inhibitors (pooled incidence rate ratio, 1.52; 95% CI, 1.06-2.19).[43] In the setting of plaque psoriasis, the long-term extension of clinical trials with TNF-α inhibitors have shown malignancy rates comparable to those of surveillance and epidemiology registries.[44-46]

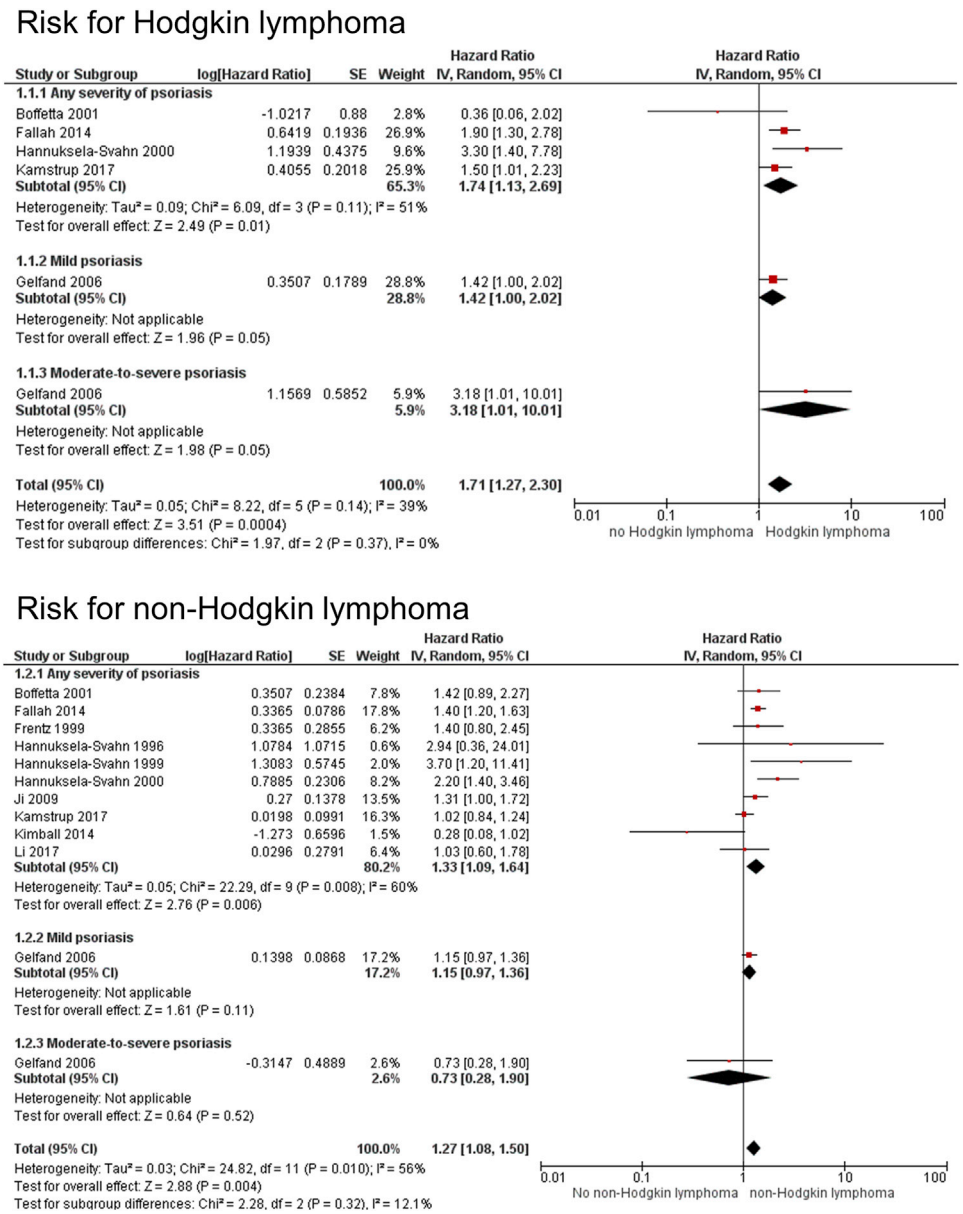

Fig 2. Forest plot for cohort studies investigating the risk of Hodgkin and non-Hodgkin lymphoma in patients with psoriasis compared to general population.

Metabolic comorbidities such as diabetes and obesity could also play a role in justifying the association between moderate-to-severe plaque psoriasis and LHMs.[38] Diabetes and obesity have been associated with a moderately increased risk of LHMs.[47] Individuals with diabetes show a relatively immunodeficient state, which may contribute to the pathogenesis of lymphoproliferative disorders; insulin and insulin-like growth factor-I can induce cell proliferation, reduced apoptosis, and even favor metastasis.[48] The metabolic and inflammatory changes resulting from obesity may increase the cell mutation rate, disturb DNA repairment, and create an environment in which pre-existing clones are permitted to emerge.[49] In addition, habitual cigarette smoking in patients with psoriasis has been associated with an increased risk of HL and NHL.[50,51]

Chronic psoriatic skin inflammation is associated with persistent T-cell activation in the skin, which increases the risk of accumulating genetic mutations and ultimately lymphomagenesis. Similarly, the sustained activation of B lymphocytes in some IMIDs may increase the risk of B-cell lymphoma, as diffuse large B-cell lymphoma in rheumatoid arthritis.[52] Local inflammatory processes are known to have

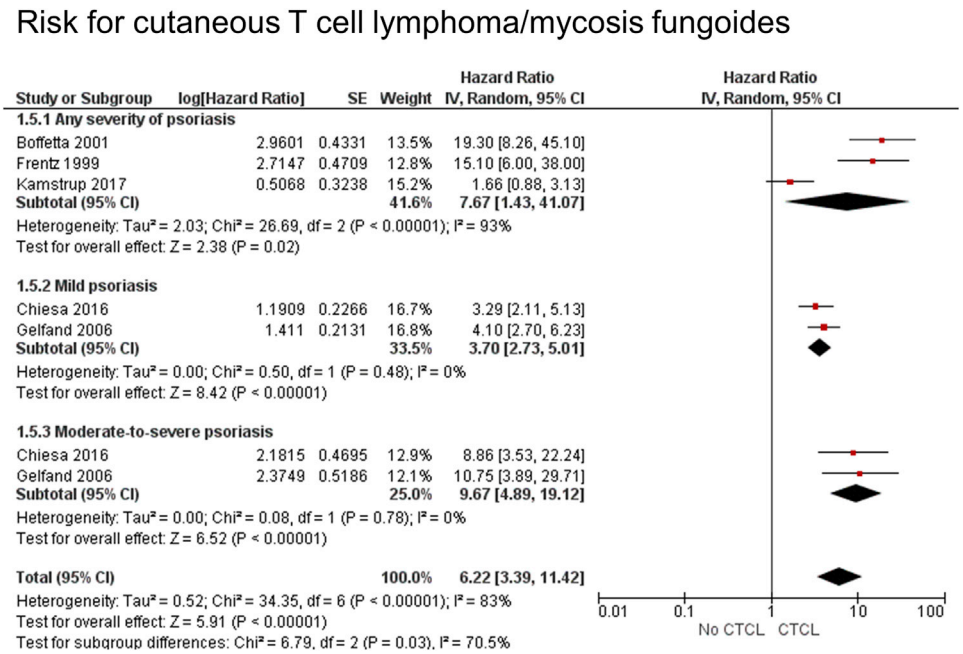

Fig 3. Forest plot for cohort studies investigating the risk of cutaneous T-cell lymphoma/mycosis fungoides in patients with psoriasis compared to general population. *CTCL*, Cutaneous T-cell lymphoma.

the potential to induce lymphoma development at the site of inflammation/immune activation. Important examples are mucosal-associated lymphoid tissue lymphomas in the context of salivary gland inflammation in Sjögren syndrome, T-cell lymphomas associated with intestinal inflammation of celiac disease, and thyroid lymphoma associated with Hashimoto thyroiditis.[52]

As T cells are the lymphocytes overstimulated in cutaneous chronic disease, a higher likelihood of T lymphoma is expected in psoriasis compared to the B counterpart. We found a positive trend between the severity of psoriasis and the risk of CTCL, supporting the hypothesis that the more-severe inflammatory burden is associated with a higher likelihood of developing cutaneous lymphoma. However, we acknowledge that only a few studies investigated the risk of LHMs in patients with psoriasis stratified according to disease severity and no studies according to disease duration.

All the phases of lymphomagenesis are potentially influenced by inflammatory mediators and cytokines, including DNA damage, altered replication, apoptosis evasion, and metastasis.[53] Different cytokines (ie, TNF-α and interleukin-6) and molecular pathway transducers (ie, signal transducer and activator of transcription 3) could activate the transcriptional factor NF-κB that may enhance tumor cell survival and proliferation.[54] A common genetic background could finally prompt patients with psoriasis to develop lymphomas, namely MF. It is worth noting that different germ-line mutations associated with psoriasis, which influence nuclear factor kappa-light-chain-enhancer of activated B cells signaling, may be found in CTCL, including TNF-α induced protein 3, TNFAIP3 interacting protein 1, BAG cochaperone 4, beta-transducing repeat containing E3 ubiquitin protein ligase, NF-κB inhibitor interacting Ras-like 2, proteasome 26S Subunit, Non-ATPase 3, and TNF receptor associated factor 2.[55,56]

There is increasing evidence suggesting that lymphomas associated with IMIDs are different entities compared to lymphomas arising in patients without any autoimmune or inflammatory condition as the 2008 World Health Organization recognized the distinct nosologic entity of diffuse large B-cell lymphoma associated with chronic inflammation.[52,57] Whether patients with psoriasis present different forms of lymphoma compared to the general population has not yet been investigated. Certain cutaneous lymphomas, particularly MF, may mimic psoriasis presenting with erythematous-desquamative plaques. The risk of developing MF in psoriatic patients has been investigated by different studies but several biases and limitations might be argued, including the not infrequent misclassification of MF as psoriasis.[58-60] A skin biopsy is required for cases in which the clinical presentation is not typical or when lesions are not responding to

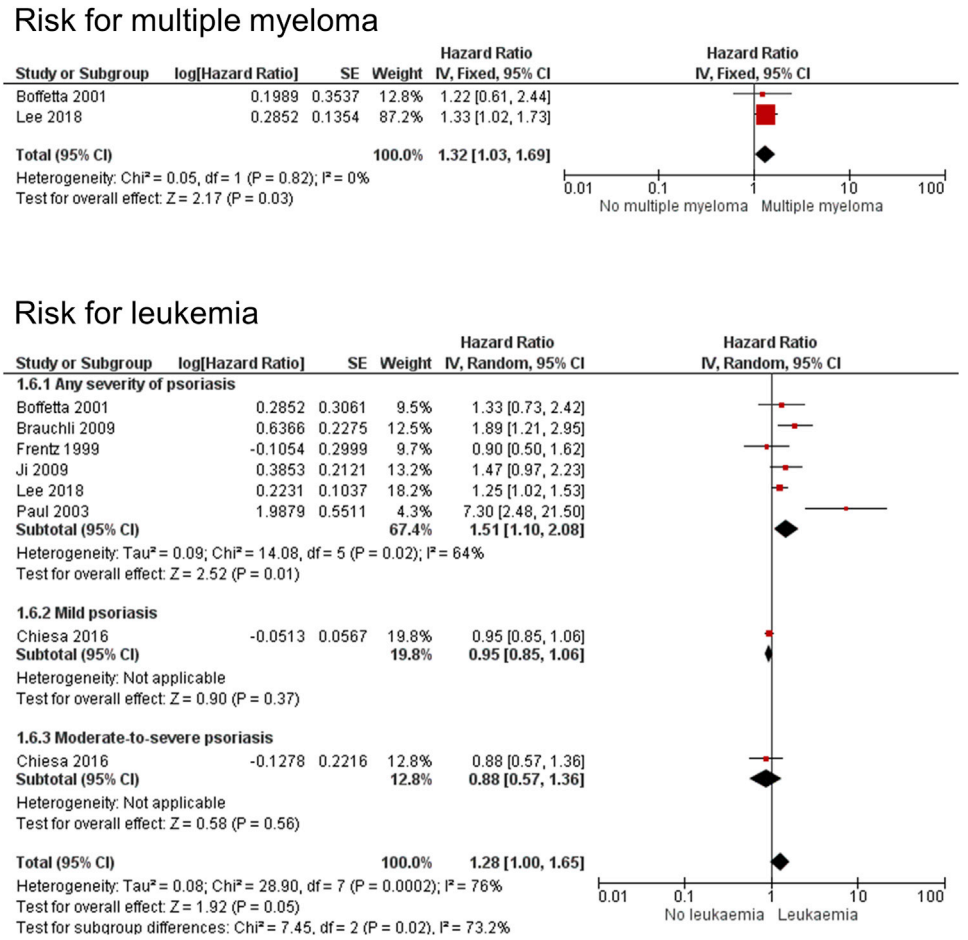

Fig 4. Forest plot for cohort studies investigating the risk of multiple myeloma and leukemia in patients with psoriasis compared to general population.

treatments.[61] Hence, the results of this study are relevant because they suggest that dermatologists should be aware of an increased risk of LHMs in patients with psoriasis, with particular attention to CTCL, particularly MF.

We acknowledge some limitations of the study: the included records may show moderate heterogeneity, which makes comparisons difficult, and different adjustments of the results were found among the included studies. Moreover, the diagnosis of LHMs and psoriasis was based on validated administrative general practitioner database in 2 studies, which can give rise to an ascertainment bias, because the diagnosis of CTCL can be challenging in a general practitioner setting.[6,20] To mitigate this issue, we conducted a sensitivity analysis, which excluded them. The sensitivity analysis confirmed the significance of the association between psoriasis and LHMs.

Data related on clinical and histopathologic records of MF, including T-cell receptor rearrangements and staging are not reported. The differential diagnosis between early MF and psoriasis may be challenging. Thus, it is possible that some patients with CTCL had been misdiagnosed as psoriasis before they were definitively diagnosed as CTCL. Two recent meta-analysis have already found a significant association between psoriasis and hematologic malignancies, but to our knowledge there are no meta-analyses investigating specifically the association of psoriasis with LHMs and their subtypes.[1,7] We did not consider a subgroup analysis among patients with psoriatic arthritis that did not show an increased risk of LHMs in the previous meta-analysis.[1,7] A strength of the study results is that we included studies involved different geographic populations (ie, European, American, and Asian).

In conclusion, this meta-analysis supports an increased risk of LHMs, particularly for CTCL/MF in patients with psoriasis, indicating the need for special attention for the emergence of cutaneous lymphoma in patients with psoriasis.

Conflict of interest

Dr Bellinato has no conflict of interest to declare. Dr Gisondi has been a consultant and/or speaker for AbbVie, Almirall, Amgen, Janssen, Leo Pharma, Eli Lilly, Novartis, Pierre Fabre, Sandoz, Sanofi, and UCB. Dr Girolomoni served as consultant and/or speaker for AbbVie, Abiogen, Almirall, Amgen, Biogen, Boeringher-Ingelheim, Bristol-Meyers Squibb, Celltrion, Eli Lilly, Genzyme, Leo Pharma, Menlo therapeutics, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, and UCB.

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